REVIEW ARTICLE

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Asthma phenotypes

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Abstract

Currently, categorization based on cluster analysis by objectively grasping the diversity of pathology is being conducted and the diversity of asthma is being categorized as phenotypes. Clinically, there is categorization based on aging and on allergic diathesis which is clinically useful; however, it has not, up to now, come to the point of selection based on phenotype. Subsequently, what is desired is the establishment of phenotype categorization for the purpose of materialization of treatment strategy which corresponds to individual cases. This study elaborates on order-made medicine while considering phenotype.

KEYWORDS

asthma, order-made medicine, phenotypes

1 | INTRODUCTION

Regarding asthma, the reactivity for progress and treatment differs for each patient and it has been advocated that it is not a single disease, but is a syndrome whereby the main complaint is asthma and dyspnea. It is thought that various genetic and environmental factors are involved and the clinical image is diverse, hence phenotype categorization based on index such as symptoms, inducement, progress, outbreak period, bronchitis, respiratory functions. However, whether these categorizations have a clinical advantage is still unclear. Recently, many etiologic genes have been reported and pharmacogenetics study has been conducted. However, at this stage, it has not come yet to the point where it can be introduced into actual medical practice, the current state is that there are still few reports on an improvement of treatment achievement through genetic analysis.

There is expectation to apply the purpose of phenotype categorization to things such as prevention of disease, control, and treatment selection.

2 | ASTHMA PHENOTYPE

Before now, phenotype categorization based on index such as outbreak age, course, severity, inducement (atopic type and nonatopic type, virus infection, etc.), reactivity to treatment (such as steroid reactivity), bronchitis, induced sputum,and FeNO (fractional exhaled nitric oxide) has been conducted. Moreover, a more objective categorization using statistical method such as cluster analysis has been applied and this study introduces representative categorization.

2.1 | Cluster analysis by Haldar et al.

Haldar et al. has categorized asthma into five phenotypes through cluster analysis by targeting a secondary care asthma group of 187 cases inclusive of heavy asthma.[1] (Figure 1).

Group 1: Early-onset atopic asthma (early age onset, atopic type): respiratory tract reversibility was both strong and especially eosinophilic inflammation was strong. Deterioration repeatedly occurs.

Group 2: Obese, noneosinophlic asthma:Inflammation is not prevalent and occurs most commonly in overweight woman.

Group 3: Benign asthma: Control of symptoms and inflammation is good and prognosis is good.

Group 4: early symptom predominant asthma (early age onset, symptom prioritization type): Both inflammation and reversibility do not occur so often and symptoms are strong and tendency toward overtreatment.
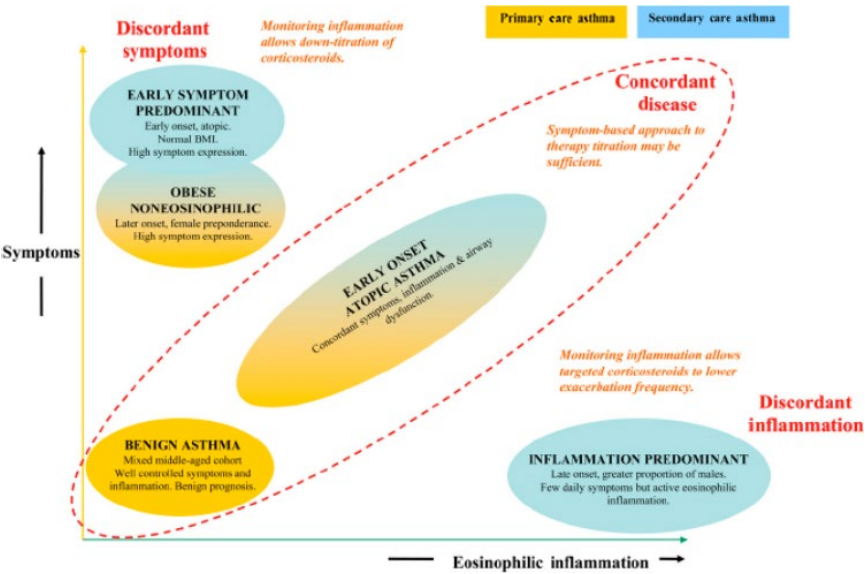

FIGURE 1 Asthma Phenotypes: Based on cluster analysis (quote from Literature 1)

Group 5: Inflammation-predominant asthma (inflammation superiority type): Eosinophil inflammation is strong, and compared to this, symptom is not so prevalent, and treatment is liable to become insufficient. Mostly occurs in men.

Haldar et al. grouped these phenotypes by index based on strength of symptoms and eosinophil types and position groups 1, 2, 4, 5, into serious asthma (Figure 1). Specifically for groups 4, 5, eosinophil inflammation is detached.

2.2 | Cluster analysis of SARP registration examples

Moore et al.[2] targeted asthma patients registered with the Severe Asthma Research Program (SARP) supported by National Heart Lung and Blood Institute (NHLB1) (over 12 years old 726 cases) and conducted cluster analysis using respiratory functionality (before infusion of bronchodilating preparations and FEV after infusion) and onset age and categorized 5 categories 2 (Figure 2).

Cluster 1: Pediatric onset type, atopic type light asthma.

Cluster 2: Pediatric onset type, atopic asthma. The largest group and compared to cluster 1 the use and dosage of long-term management drugs is big.

Cluster 3: Adult-onset type, primarily nonatopic type, relative age is and mostly women. BMI is an average of 33, many obese patients can be considered equivalent to phenotype 2 group (obese, noneosinophilic asthma) categorized by Haldar et al.

Cluster 4: Pediatric onset type, atopic type, serious asthma. Can be considered as equivalent to phenotype 1 (early-onset atopic asthma) as categorized by Haldar et al.
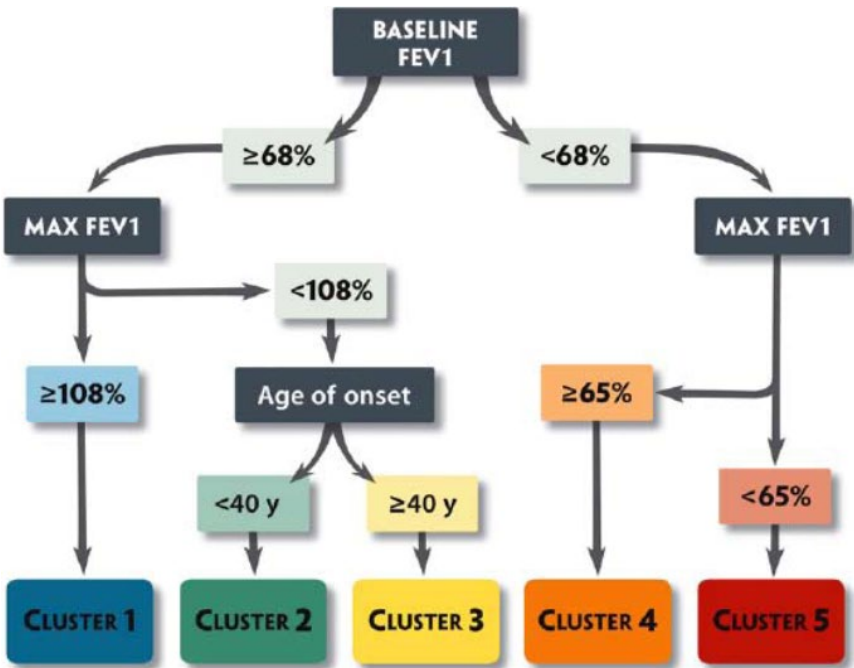

FIGURE 2 Tree analysis Categorization based on cluster analysis of U.S. Severe Asthma Research Program (quote from Literature 2)

TABLE 1 Clinical characteristics, diagnosis, and treatment of asthma phenotypes (severe phenotypes based on cluster analysis by Haldar et al.)

Clinical characteristics of asthma phenotypes (severe phenotypes based on cluster analysis by Haldar et al.)	Clinical features in the diagnosis	Treatment strategy for each severe asthma phenotype
Group 1, Early-onset atopic asthma: Airway reversibility and airway inflammation, especially in eosinophilic inflammation, are significant. Repeated exacerbation is often observed	Atopic dispositions and eosinophilic inflammation (increased sputum eosinophil count and increased FeNO)	Enhanced treatment of eosinophilic inflammation is required. Increase in ICS, LTRA (leukotriene receptor antagonists) administration, anti-IgE antibody therapy, and monitoring of adherence
Group 2, Obese noneosinophilic asthma: Lack of eosinophilic symptoms. Often seen in obese women	Decreased lung function due to obesity	Weight control is required for lung dysfunction due to obesity
Group 4, Early symptom predominant asthma: Lack of inflammation and reversibility. Symptoms are significant. A risk of overtreatment	Lack of eosinophilic inflammation. Absence of increase in sputum eosinophil count or FeNO. COPD may be present	Eosinophilic inflammation is likely to be predominant. Administration of bronchodilator LABA (long acting β2 agonists) or LAMA[a] (long-acting anticholinergic drug)
Group 5, Inflammation predominant asthma: Eosinophilic inflammation is significant, but symptoms are less significant. A risk of undertreatment. More observed in men	Eosinophilic inflammation (increased sputum eosinophil count and increased FeNO)	Enhanced treatment of eosinophilic inflammation is required. Increase in ICS, administration of LTRA etc., and monitoring of adherence

[a]Tiotropium.

TABLE 2 Clinical characteristics, diagnosis, and treatment of asthma phenotypes based on cluster analysis of the U.S. Severe Asthma Research Program

Clinical characteristics of asthma phenotypes based on cluster analysis of the U.S. Severe Asthma Research Program (SARP)	Clinical features in the diagnosis	Treatment strategy
Cluster 1: Early-onset atopic asthma. Mild symptoms of asthma	Atopic dispositions and eosinophilic inflammation (increased sputum eosinophil count and increased FeNo)	Administration of a low or medium dose of ICS or LTRA
Cluster 2: Early-onset atopic asthma (the largest cluster). Increased use of controllers compared with Cluster 1	Atopic dispositions and eosinophilic inflammation (increased sputum eosinophil count and increased FeNo)	Enhanced treatment of eosinophilic inflammation is required. Increase in ICS, LTRA administration, and monitoring of adherence
Cluster 3: Late-onset asthma. Less likely to be atopic. Mostly older obese women (the mean BMI is 33). This cluster is equivalent to Group 2 by Haldar et al.	Decreased lung function due to obesity	Weight control is required for lung dysfunction due to obesity
Cluster 4: Early-onset atopic asthma. Severe symptoms of asthma. This cluster is equivalent to Group 1 by Haldar et al.	Eosinophilic inflammation (increased sputum eosinophil count and increased FeNo)	Enhanced treatment of eosinophilic inflammation is required. Increase in ICS, LTRA administration, anti-IgE antibody therapy, and monitoring of adherence
Cluster 5: Late-onset atopic asthma. Severe symptoms of asthma. Less responsive to bronchodilators. Chronic airflow obstruction	Eosinophilic inflammation (increased sputum eosinophil count and increased FeNo)	Enhanced treatment of eosinophilic inflammation is required, Increase in ICS, LTRA administration, anti-IgE antibody therapy, and monitoring of adherence

Cluster 5: Adult-onset type, atopic type, serious asthma. Even with the use of bronchodilating preparations, respiratory functions do not sufficiently improve with many patients indicating continuous airflow restrictions.

The categorization by Moore et al. is practical in the sense that it is a cluster analysis which is a simple method using only onset age and FEV and the result is similar to the category of Haldar et al.

The author summarized the clinical characteristics, diagnosis, and treatment of asthma phenotypes based on cluster analysis by Haldar et al. in Table 1 and asthma phenotypes based on cluster analysis of the U.S. Severe Asthma Research Program (SARP) in Table 2.

3 | ASTHMA TREATMENT OF PHENOTYPE CATEGORIZATION

As there exist diverse phenotypes for asthma, treatment selection should be made which is in line with clinical characteristics and individual patients' background. Order-made medicine which provided

the best treatment for individual patients is essential and whether or not order-made medicine can be applied to phenotype is elaborated below.

3.1 | Eosinophil type asthma, noneosinophil asthma comparison:

From the standpoint of phenotype categorization or cluster analysis, the existence of onset age, natural progress, the existence of causative factor of atopy is an important factor and specifically from the standpoint of treatment selection, as a phenotype for reference, attention is focused on eosinophil asthma and noneosinophil[3] McGrath et al. analyzed the results of induced sputum examination for 995 cases of light to mid-range asthma, and indicated that for patients without treatment of ICS (inhaled corticorteroid), about half also corresponded to noneosinophil asthma. With medication of prednisolone (0.5 mg/kg/d), budesonide 800 μg twice a day, zafirlukast 20 mg twice per day, to treat anti-inflammation for 10-14 days, in noneosinophil patients, the airflow restriction did not improve. On the other hand, the bronchodilating effect with the use of B2 stimulant drug was similarly recognized in noneosinophil and eosinophil asthma. This result shows that the number of eosinophil through induced sputum examination is useful in the selection of asthma treatment.

3.2 | Asthma with allergic rhinitis

Allergic rhinitis is frequently associated with adult-onset asthma. Tanimoto et al.[4] compared the time of onset between the two conditions and reported that the onset of allergic rhinitis was 9.7 years earlier on average than that of asthma in adult patients with asthma with age 30 years or older. In 2009, a nationwide study in Japan (SACRA survey) reported that 67.3% of adult patients with asthma had allergic rhinitis.[5] As allergic rhinitis is frequently associated with asthma and may affect the control of asthma, we consider that LTRA and Th2 cytokine inhibitor are useful to improve the symptoms of asthma and rhinitis.

3.3 | About refractory asthma

As for refractory asthma based on asthma prevention・ management guideline 2012, even when treatment step 4 treatment is conducted, it is positioned that it is asthma which belongs to the most serious continuous type whereby symptoms occur every day. Refractory asthma continues for a long time and occurs in nonatopic type for adult occurrence type and risk factors include female gender, obesity, smoking, and aspirin sensitivity, and it assumes 10-15% of adult asthma patients and treatment is extremely difficult. As for refractory asthma phenotype, the aggravation of frequency of occurrence, the irreversibility of airflow restriction, steroid dependency, and resistance is crucial. However, as for phenotype which is effective for reactivity against prognosis and treatment, there are only a few which are established, and through analyzing these phenotypes, attempt is made to categorize the disease types.

3.4 | Anti-IgE antibody treatment against atopic type refractory asthma

Among high-dose ICS and LABA, LTRA, theophylline sustained release tablet, even with the combined use of two types, when control was not good, an oral steroid drug was used. Currently, there is high recognition of the effect of the use of molecular target drug anti-IgE monoclonal antigen (omalizumab). As for omalizumab, it is positive for perennial inhalation antibody, and the serum total IgE value 30-700 IU/mL serious cases are applicable and it combines with isolated IgE antibody Cr3 and by controlling activation of IgE of inflammatory cell such as mast cells, it is used in the treatment of refractory asthma. The effectiveness rate is 60%, and there is a need for more research on responder selection method for omalizumab to enhance the treatment effect.

3.5 | About LTRA-resistant asthma

In about 30% of asthma patients, there is genetic polymorphism of LTC4 synthesis enzyme, and there is difference in LTRA effect.[6] However, normally it is difficult to measure LTC4 synthetic enzyme gene. Even with a dosage of furuchikazone (FP200-4—μg/d) for those where control cannot be achieved for mid-range and heavy range continuation type LTRA resistance adult asthma patients, when giving medication of Th2 cytokine inhibitor drug, effect was achieved. From the perspective of personalized medicine, it can be thought that to give cytokine inhibitor drug for LTRA resistance adult asthma, could be a choice.

3.6 | About aged asthma

It has been diagnosed that among those over 65 years of age, 4-13% have cancer; however, the diagnosis of asthma in the aged is not yet sufficient. Moreover, it seems that the mortality rate among aged asthma patients is due to insufficient treatment, aggravation of adherence, and many other causes such as complications. However, the possibility of immunosenescence has been indicated.[7] When categorizing aged asthma based on onset period, it can be categorized into continuation of pediatric asthma, long-standing/childhood-onset asthma which reoccurs after remission, and late onset asthma.[8] Busses has, regardless of onset period, indicated that immune aging is in the background of aged asthma. Moreover, there are three risk factors of respiratory function deterioration, for both men and women, which are aging, smoking, and asthma. Comparing asthma which occurs in those aged over 65 and in nonaged asthma, in aged asthma, the decline with age the flow of volume in one-second is large and although respiratory tract reversibility was seen, in nonaged onset, there was a remarkable deterioration of respiratory function. Respiratory tract indicated reversible response and remodeling impact was implied.[9] Moreover in aged onset, night symptoms were small and seasonality was seen mostly during the winter, and the most common feature was COPD (chronic obstructive pulmonary disease). On the other hand, in nonaged onset, there were high incidence of night symptoms and

TABLE 3 Tailor-made treatment based on asthma phenotype classification

Classification of asthma phenotype	Tailor-made treatment
a) Eosinophilic asthma, noneosinophilic asthma	Eosinophilic asthma: Increase in ICS, LTRA administration etc. Noneosinophilic asthma: Administration of bronchodilator LABA or LAMA
b) Asthma with allergic rhinitis	In addition to ICS, treatment with LTRA and Th2 cytokine inhibitor are to be considered
c) Refractory asthma	Specific treatment for each condition is required for patients with refractory asthma because a variety of complications and exacerbating factors should be considered in the treatment
d) Refractory atopic asthma	Administration of anti-IgE monoclonal antibody (omalizumab)
e) LTRA-resistant asthma	Administration of Th2 cytokine inhibitor, etc.
f) Asthma in the elderly	Monitoring of adherence and instruction of inhalation therapy are most important Early introduction of ICS for prevention of death due to asthma Additional administration of LAMA (tiotropium) for asthma patients with and COPD Introduction of ICS with small particle size to reduce the distal airway inflammation Treatment while controlling the systemic disease

seasonality occurred mostly during spring. Also atopic causative factors were involved and daily fluctuation was seen as being large.[10] For further clarification, the authors showed the pathology of aged asthma; among asthma patients more than 65 years old and above for which the onset age is clear, cases without smoking history were separated into nonaged onset group (15 cases) and those aged onset group over 65 years old (15 cases). As a result of comparative discussion about IOS (impulse oscillation system), level of severity, atopy causative factor, inflammation of respiratory tract and spirometry, the level of severity was, compared to the nonaged onset type, aged onset group the number of light cases was of an increasing tendency. In aged onset asthma as well, the involvement of atopy causative factor existed and in respiratory tract inflammatory marker, there was no significant difference based on onset age. As for level of urgency, compared with nonaged onset group, with aged onset group, there was higher tendency of light cases. Among aged onset asthma as well, there existed involvement of atopic causative types and with respiratory tract inflammation marker, there was no significant difference in onset age. As for respiratory refractability, regarding respiratory tract sensitivity, there was no significant difference in onset age. Moreover, from the standpoint of spirometry IOS results, regarding aged onset asthma over 65 years of age, it was indicted that there is possibility for respiratory functionality and decline with age of peripheral respiratory impediment to progress in a comparatively short period. The symptoms of aged asthma are slight, and there is need to be sufficiently careful of diagnosis. To prevent asthma death in the future, it is thought that ICS early introduction is required. However, for aged asthma, in addition to respiratory function and deterioration in physiological function, treatment has become difficult due to deterioration in adherence due to a decline in the level of understanding and memory, and as for midaged onset type patients, compared with young onset type patients, there is less experience in terms of treatment, and in the handling inhalation devices. As progress in the selection of treatment drugs is expanding and inhalation devices are diversifying, it can be seen to complicate the acquiring of inhalation method. With the aged, there is high involvement of peripheral respiratory tract issues and there is the possibility that inhalation drugs will not reach the peripheral respiratory tract. Therefore, it is thought that inhalation should be conducted regularly.

The author presented a proposal for tailor-made treatment for asthma phenotypes described in a) to f) in Table 3.

4 | CONCLUSION

The phenomenon of asthma is very heterogeneous and is recognized as not a single disease but is a syndrome with asthma and respiratory difficulty as a main complaint. It can be thought that with each phenotype, there is a need for an order-made medicine in accordance with each patient. When a sufficient treatment result cannot be attained although appropriate treatment is conducted, before serious asthma is assumed, it is important to think of the causes based on each phenotype such as environmental factors, complications, drug resistivity, confirmation of treatment adherence, mistakes in inhalation method. In this regard, there is a great need to consider phenotype elements for order-made medicine.

In conclusion, phenotype is based on clinical symptoms such as respiratory function, onset age, blood biochemical examination values; the end type is categorization based on genes and molecular biological mechanism, and although it has been clarified that for asthma there are diversified phenotypes, however, in the background, it is thought that there exist diversified end types. It is expected that end type and phenotype related should be elucidated and order-made treatment appropriate for each individual patient be made possible. Currently, we are groping for a way toward treatment selection based on phenotype; however, we have not yet come to the point of selecting the appropriate treatment for all. Specifically, there are serious, difficult-to-cure cases for aged asthma. There are also issues of asthma death which might be prevented based on finding the best ways possible for device selection and in the improvement of adherence.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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